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### **A tailored mHealth intervention for improving treatment adherence for people living with HIV in Iran (HamRaah)**

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# BMJ Open Tailored mHealth intervention for improving treatment adherence for people living with HIV in Iran (HamRaah): protocol for a feasibility study and randomised pilot trial with a nested realist evaluation

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## ABSTRACT

**Introduction** Middle East and North Africa (MENA) has a rising rate of new HIV infections and AIDS-related mortality. Consistent adherence to antiretroviral therapy (ART) leads to viral suppression, preventing HIV transmission and treatment failure. mHealth interventions can improve ART adherence by providing tailored support and directing patients to existing healthcare services. HamRaah (Persian for ‘together-in-path’) is the first mHealth-based intervention in a MENA country and is designed to improve adherence through two-way mobile messaging for people recently diagnosed with HIV in Tehran, Iran. The objectives of this pilot randomised controlled trial (RCT) are to examine the feasibility, acceptability and preliminary effectiveness of HamRaah, and to develop an explanatory theory for any observed effects through a nested realist evaluation.

**Methods** A feasibility study and two-arm RCT of HamRaah, with an embedded realist evaluation will be conducted. Participants will be randomised 1:1 to HamRaah or routine care for a 6-month intervention. The initial effectiveness of HamRaah will be assessed through the primary outcome of self-reported ART adherence and several secondary outcomes: retention in care, CD4 count and viral suppression. A theory-driven realist evaluation framework will be used to develop an explanatory theory regarding what works, for whom, how and in what context.

**Ethics and dissemination** The study received ethical clearance from Tehran University of Medical Sciences Ethics Committee and Oxford Tropical Research Ethics Committee. People living with HIV in Tehran and key country stakeholders in HIV policy and programming have been involved in the development of HamRaah and this pilot trial. Participants will provide informed consent prior to study enrolment. The results will be disseminated to all stakeholders and presented in peer-reviewed journal publications and conferences.

**Trial registration number** IRCT20100601004076N23; Pre-results.

## Strengths and limitations of this study

- This pilot randomised controlled trial of mHealth for adherence to antiretroviral therapy is the first of its kind in a Middle East and North Africa (MENA) country. It addresses an important evidence gap with regards to the feasibility, acceptability and potential for impact of a tailored mHealth approach within MENA.
- The study uses triangulation of quantitative, qualitative, and realist data to produce complimentary findings and a deeper understanding of the role of context.
- Patients and public stakeholders were consulted in the design of the mHealth intervention, and in trial planning and implementation.
- This pilot study is designed to provide an initial estimate of effect size, but may have insufficient statistical power to detect differences in outcomes between groups.
- The intervention period will be relatively short, limiting the capacity to show long-term effects that might accumulate over time.

## INTRODUCTION

Despite the expansion of antiretroviral therapy (ART), countries in the Middle East and North Africa (MENA) region continue to show an increasing rate of new HIV infections and AIDS-related mortality.<sup>1</sup> Only 32% of people living with HIV (PLHIV) are virally suppressed, compared with 59% globally.<sup>1 2</sup> Consistent ART adherence promotes viral suppression and maximises the benefits of treatment as prevention,<sup>3</sup> which is essential for both PLHIV and the public. Conversely, non-adherence is a major contributor to poor viral suppression,<sup>4–7</sup> ultimately leading to treatment failure<sup>8</sup> and increasing morbidity

and mortality.<sup>9 10</sup> Thus, programmes are needed to support PLHIV who are receiving ART, to achieve consistently high adherence to daily medication regimens.<sup>11–15</sup>

Over the past two decades of ART expansion, a variety of adherence interventions have been tested and shown to be effective and sustainable in both high-resource and low-resource settings.<sup>16 17</sup> Interventions that build on existing healthcare infrastructure and leverage available resources to support PLHIV are particularly useful.<sup>18</sup> A promising strategy involves interventions delivered through mobile and digital platforms. Rather than devoting additional resources for conventional programmes, connecting PLHIV digitally to existing programmes can potentially support ART adherence with increased personalisation and scale at a lower cost.<sup>19–21</sup> WHO recommends mHealth strategies for improving ART adherence,<sup>22</sup> but emphasises that mHealth interventions are better suited to support rather than replace health services,<sup>18</sup> and highlights the need for tailored and differentiated models of care delivery.<sup>23</sup>

HIV differentially affects key population groups, such as people who inject drugs (PWID), sex workers and their clients, men who have sex with men, transgendered individuals and the general population.<sup>24</sup> This heterogeneity of the HIV epidemic has propelled a paradigm shift, calling for differentiated care models to manage HIV.<sup>23 25</sup> Moreover, in dealing with highly vulnerable segments of the population, experts caution against transporting interventions across groups, regions and countries, and recommend interventions that fit regional, national and local contexts.<sup>26 27</sup> This concern is especially salient with regards to the MENA region, where high levels of HIV-related stigma and discrimination<sup>28 29</sup> require programmes to respect privacy concerns. Moreover, the current COVID-19 pandemic necessitates minimising hospital visits and increasing remote service delivery. Digital interventions, with their potential for increased personalisation and privacy, can offer remote and differentiated HIV care suited for the MENA context, provided that PLHIV have personal access to mobile phones, and that providers can ensure data security. There is, however, a dearth of evidence on interventions that have been adapted and tested specifically for MENA countries. Thus, interventions with fidelity to the evidence-base and adaptation to this specific context are needed.

In response to this need, and for the first time in a MENA country, this study aims to examine the feasibility, acceptability and preliminary effectiveness of an mHealth intervention in Tehran, Iran, with an emphasis on the role of context to discover how, for whom, and why the intervention works (or not), using a nested realist approach.<sup>30</sup> Home to 29% of all cases in the MENA region,<sup>1</sup> HIV prevalence in Iran is estimated at 0.05%.<sup>31–33</sup> As opposed to the rest of MENA, the rate of new HIV infections in Iran has declined by 12% since 2010. This improvement could be attributable to the healthcare infrastructure, which provides access to methadone replacement therapy, needle exchange programmes, free and universal access

to ART at the point of diagnosis, and peer-run adherence clubs to support PLHIV throughout every province in the country. This combination of services provides the optimal setting for an mHealth intervention that leverages existing healthcare capacities.<sup>34 35</sup> By 2018, Iranians had been assigned over 169.5 million SIM cards, of which 88 million were actively in use for a population of 81.8 million,<sup>36</sup> thus making text-messaging a widely accessible form of communication. Smartphone use has also rapidly increased over the past 3 years, and the country is now 11th in the world in terms of smartphone penetration rate.<sup>37</sup> Iran is also severely hit by the COVID-19 pandemic within the MENA region, further necessitating the assessment of healthcare approaches that minimise physical hospital visits. Thus, mHealth interventions that offer remote support, safely and effectively, could be a promising approach to address the challenges of managing HIV.

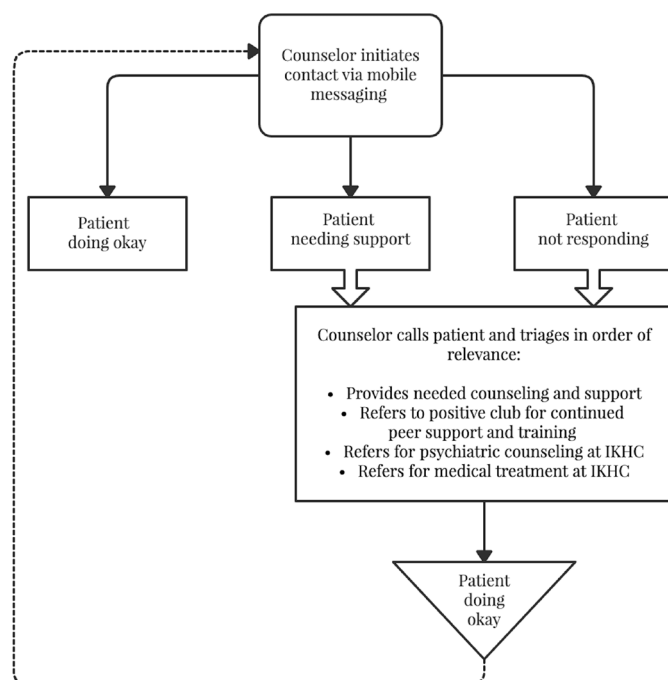
### HIV epidemic in Iran

The HIV epidemic in Iran was initially interwoven with the injection drug use epidemic, but currently incidence is mainly driven by sexual transmissions.<sup>38</sup> Recently, the epidemic burden is shifting from men to women. Before 2017, 65.8% of transmissions occurred through the use of shared needles by PWID, the largest key PLHIV, while sexual and vertical transmissions accounted for 19.6% and 1.5% of all cases, respectively. Since 2017, 47% of cases were sexually transmitted, followed by 32% of cases of transmission through injection. The total proportion of women diagnosed with HIV increased from 4.7% of all cases in 2001 to 16% in 2017.<sup>34 39 40</sup> Iran provides universal and free access to ART through a decentralised model of health delivery across 31 provinces via university hospitals, operating under the joint Ministry of Health and Medical Education, providing uniform services for HIV, such as voluntarily, counselling and testing (VCT) centres and Positive Clubs.

### Intervention rationale

Two-way communication approaches appear to have important benefits for improving ART adherence and achieving viral suppression. WelTelKenya<sup>41</sup> was the first study supporting PLHIV through weekly text-message check-ins, and in a similar study in Uganda,<sup>42</sup> weekly, but not daily, communication improved adherence. Meta-analyses corroborate that two-way and weekly messaging interventions appear more effective and less burdensome than daily one-way reminders.<sup>43 44</sup> Moreover, recent studies show that mobile messaging may not be effective for PLHIV starting second-line therapy as a result of non-adherence,<sup>45 46</sup> suggesting that mHealth interventions may be more effective when implemented at the onset of ART to promote better habit formation<sup>47</sup> and improved long-term outcomes, although the long-term effectiveness has not been studied beyond a year.

HamRaah (Persian for 'together-in-path') is a two-way mobile messaging intervention, depicted in [figure 1](#), for



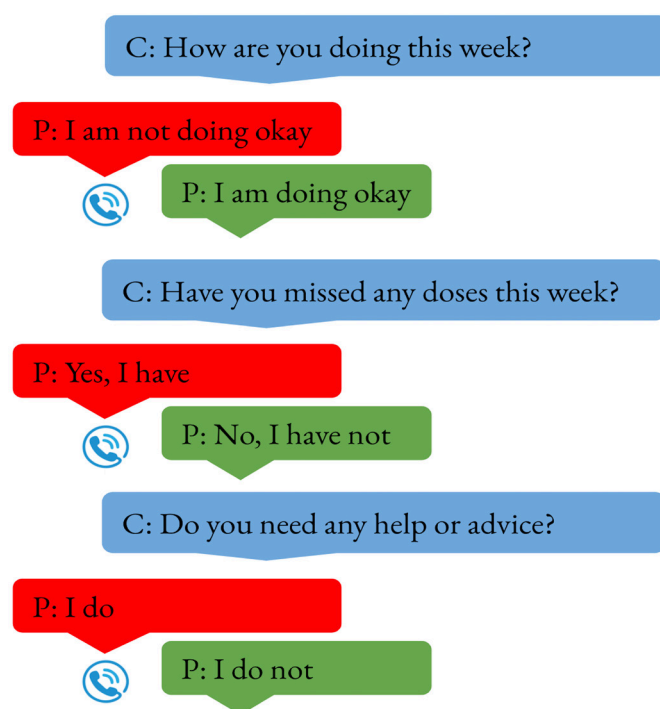
**Figure 1** HamRaah intervention protocol. IKHC, Imam Khomeini Hospital Complex.

recently diagnosed PLHIV in Tehran, Iran. An initial qualitative study investigated the Iranian context in which HIV is managed. The findings (currently under review for publication) signified that high levels of stigma and discrimination lead to loss of hope and motivation to adhere, especially within the first year following diagnosis, when navigation of the health system and access to available resources is also unfamiliar. During this period, mHealth interventions can make PLHIV feel cared for by offsetting depressed mood,<sup>47</sup> and increase motivation for adherence through positive reinforcement.<sup>23</sup> Moreover, by providing an efficient means of connecting patients to needed care before they reach a critical clinical stage, either from non-adherence or untreated comorbidities, such interventions may reduce mortality and save costs for the health system.<sup>25</sup>

## AIMS AND OBJECTIVES

The current pilot study's overarching aims are to examine HamRaah's: (1) trial feasibility and intervention acceptability, (2) initial effectiveness and (3) explanatory theory. The specific objectives are as follows:

1. Assess the feasibility of recruitment, randomisation, allocation concealment and blinding procedures for outcome assessment.
2. Determine the acceptability of HamRaah intervention by participants and fidelity to protocol by counsellor.
3. Determine preliminary effects of the pilot intervention on the primary outcome of adherence to ART.
4. Conduct a nested realist evaluation to refine an explanatory programme theory with enriched evidence on what works, for whom, how and in what circumstances.



**Figure 2** HamRaah Weekly messaging protocol, C: Counsellor, P: participant, red responses will trigger a phone call.

5. Triangulate realist, qualitative and quantitative findings in a sequential approach to investigate mediating relationships.

Reporting in this protocol is based on the Standard Protocol Items: Recommendations for Interventional Trials checklist for recommended items in a trial protocol.

## METHODS AND ANALYSIS

### Overview of study design

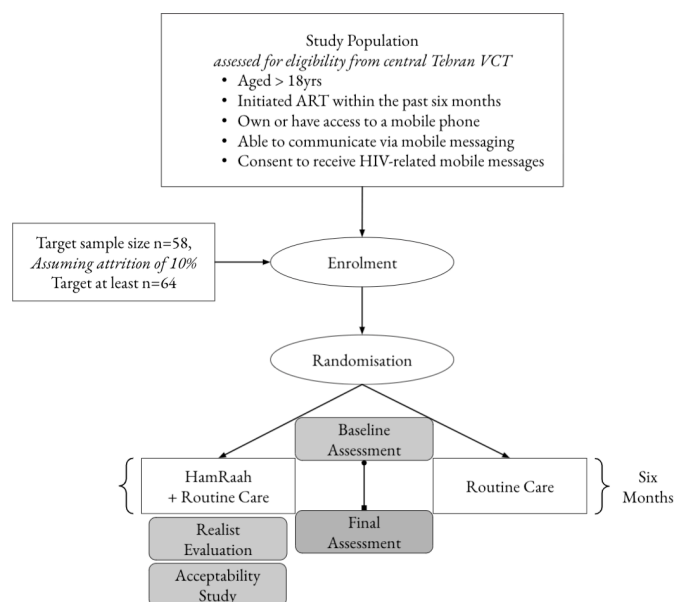
The feasibility and acceptability study relate to procedural uncertainties of the trial and the acceptability of HamRaah. These aspects will be examined via quantitative and qualitative data, collected throughout the implementation process and at the conclusion of the trial through checklists, spreadsheets, focus group discussions (FGDs) and interviews. The perspectives of HamRaah participants, counsellor and project staff will be collected to answer the feasibility and acceptability questions that could inform a future definitive trial.

The HamRaah pilot consists of:

- Arm1: routine care +HamRaah.
- Arm2: routine care.

Participants will be assigned through permuted even-number blocks to be randomised in a 1:1 ratio to arm 1 or arm 2. The intervention period is 6 months for each participant in arm 1, with equivalent follow-up for participants in arm 2. Figures 1 and 2 represent the intervention and messaging protocol respectively. The initial effectiveness of HamRaah will be assessed through self-reported ART adherence, as a primary outcome, and retention in





**Figure 3** Study design. ART, antiretroviral therapy; VCT, voluntarily, counselling and testing.

routine clinical care, immune reconstitution and viral suppression, as secondary outcomes. **Figure 3** provides the study design, flow, criteria for selection of participants and outcome assessment points.

The nested realist evaluation will be informed by HamRaah participants through mechanistic thinking, which aims to develop an explanatory theory of how and why HamRaah may work (or not).<sup>30 48</sup> Thus, the focus of the nested realist intervention will be to recognise which aspects of the study context are changed through HamRaah, and how this change could alter participants' reasoning, triggering a new mechanism and producing an observed outcome, explained in a refined theory.

### Research setting

The study will be conducted in the infectious diseases unit of the Imam Khomeini Hospital Complex (IKHC), which is the teaching hospital of Tehran University of Medical Sciences (TUMS) and based in the sociodemographically diverse city centre of Tehran. IKHC houses Tehran's central VCT centre, where the study participants will be recruited from the VCT's more than 4000 patients and an average of 15 new cases of monthly HIV diagnosis. A peer-run Positive Club at IKHC offers peer-delivered counselling and psychosocial support for PLHIV who need additional care. IKHC also houses the Iranian Research Centre for HIV/AIDS (IRCHA)—the main collaborating research partner of this project—with a team of eight full-time researchers and research assistants, from which the staff for this project are recruited. For additional information see online supplemental appendix 1.

### Routine care

Routine care offered at the VCT centres consists of an initial general counselling session at the time of diagnosis. Medication pick-up is initially set at a monthly

interval, and as patients collect medications regularly, and appear to be adhering well, the window for collection is extended to every 2 months. However, as a result of the recent pandemic, this time frame has been extended to reduce patient visits to the hospital, now collecting their medications every 3–6 months, while some receive their medications via motorcycle delivery system. For additional information see online supplemental appendix 1.

### HamRaah intervention

HamRaah is a weekly mobile messaging intervention, based on the WeTel model,<sup>41 49</sup> which serves as a counsellor-initiated check-in with recently diagnosed PLHIV to assess adherence and physical and mental well-being in the past week. **Figure 1** depicts the key features of the HamRaah protocol, which are offered in addition to the routine care outlined above. HamRaah recipients will be contacted by text message on a weekly basis by a counsellor to enquire about their well-being and adherence to ART. The counsellor specifically asks PLHIV how many (if any) days they missed their doses, and what (if any) problems they may be facing. If contacted, PLHIV do not respond to the messages, or report back on missing doses or facing challenges, a follow-up contact by live phone call will be made to assess the patient's current needs. **Figure 2** is a pictorial representation of the weekly messaging protocol. For additional information see online supplemental appendix 1.

### Research population

Newly identified PLHIV, enrolled under care at the VCT centre, will be eligible to participate if they meet the following criteria: (1) are aged 18 years or above; (2) are treatment naïve, defined as starting ART within the 6 months; (3) own or have access to a mobile phone; (4) are able to operate a cell phone to communicate using mobile-messaging (help by a partner is sufficient for patients with reading and/or writing difficulties); (5) consent to be contacted through mobile communication to receive HIV- and ART-related information. **Figure 3** depicts the selection and flow of participants through the study.

### Sample size

This study is designed as a pilot. The target sample size of 58 is based on the number needed to detect a 20% improvement in the primary outcome of mean adherence, which will be measured as a continuous variable based on the number of missed doses. Our calculations were estimated using PS software by Vanderbilt University, and assumed a 75% baseline estimate of adherence, based on clinician estimations from pharmacy refill data, with 90% power and a two-sided alpha of 0.05; we also allowed for 10% attrition. However, the clinical significance of any observed improvement will depend on the baseline level of adherence, and smaller effects, observed within the range of 5%–10%, would also be suggestive of impact to be assessed in a fully powered study.

## Participant recruitment

Study recruitment began in August of 2019 and has faced delays due to the COVID-19 pandemic. Participants are identified from the list of HIV patients, who are diagnosed within the past 6 months and meet eligibility criteria. The IRCHA, where the research team is based, is located within the same hospital complex. All staff members conducting the recruitment and informed consent process are recruited from IRCHA, trained in the ethical treatment of human participants, and familiar with informed consent guidelines. To maximise recruitment, two approaches will be used:

- i. Direct, which involves obtaining contact information of the recently diagnosed PLHIV and contacting them via telephone to invite them to participate.
- ii. Indirect, which involves a brief introduction during individual clinic visits.

Patients who show initial interest will be asked to visit IRCHA to receive further information about the trial and provide informed consent.

## Randomisation and blinding

Randomisation procedures follows a permuted block technique, which occurs after baseline data collection. R software is utilised by a researcher in Oxford to produce a set of randomly generated assignments through permuted even-number block sizes that will randomise in a 1:1 ratio to HamRaah or routine care. A study team member in Tehran allocates participants to intervention and comparison groups based on the order of completing the informed consent forms, and the predetermined assignments received from the researcher in Oxford. This process reduces the potential for allocation bias through correct sequence generation. Researchers will notify each participant individually about his/her allocation.

Given the mHealth nature HamRaah, participants and intervention facilitators cannot be blinded to group assignments. Similarly, researchers conducting the nested realist evaluation will be aware of participant assignments. To mitigate against interviewer bias, participants will be encouraged to complete the questionnaires online. In cases where participants need assistance in completing the questionnaires, interviewer bias will be minimised by keeping the interviewers blinded to the group allocations of the participants. Any incident of unblinding will be recorded and the interviewer's knowledge regarding group assignment will be documented.

## Data collection

Quantitative data for efficacy outcomes will be collected via Research Electronic Data Capture (REDCap) at baseline and at the end of the 6-month intervention. Participants can choose to complete and submit the forms within the privacy of their homes on their mobile phones, tablets or computers. For PLHIV who need assistance in completing the survey, research assistants will arrange an appointment to guide them through the process using a computer at IRCHA. Should a participant prefer to stay

at home, the research assistant will provide guidance over the phone. For participants who prefer not to fill in online questionnaires, a paper questionnaire option will also be available.

Qualitative data, for the realist evaluation and for the acceptability study, will draw on the perspectives of HamRaah participants, lead counsellor and other providers for care to participants referred from HamRaah. The research method will involve interviews and FGDs, both of which allow researchers to explore areas of interest. Individual interviews allow an in-depth exploration of personal and sensitive topics, while focus groups involve group interactions with the possibility of creating a trusted environment among peers.<sup>50</sup> Qualitative data collection occurs at the conclusion of the 6-month intervention for participants. The initial target is to conduct five small FGDs (5–7 participants each), and 12 individual interviews (including providers). However, recruitment for focus groups and individual interviews will continue until data saturation is reached, or until all who received 6 months of HamRaah have been interviewed.

Data collection for quantitative surveys will end by May of 2021. The post-trial qualitative acceptability assessments and realist evaluation will be completed by August of 2021.

## Outcome measures

### Feasibility measurements

Feasibility outcomes of interest, relating to methodological and procedural uncertainties, are listed in [table 1](#).

### Primary outcome

#### Adherence to ART

The primary outcome of the pilot trial is adherence to daily ART, which will be measured as a continuous variable of self-reported adherence using the Wilson three-item self-report scale on adherence.<sup>51</sup> The scale will measure the number of missed doses in the past 30 days.

### Secondary outcomes

#### Retention in care

Retention in care will be measured as visit constancy for monthly (or bimonthly) appointments. Evidence suggests that there is no gold standard tool to measure retention in care and selection of approach must be tailored to context.<sup>52</sup> Larger windows for pick up are generally reserved for adherent patients; however, in the current context of the COVID-19 pandemic, medications are either being delivered to patients, or given for a longer period of time. As such, measuring the percentage of expected visits that were attended, within a 1-week window, accommodates the variability in scheduling as a result of personal or COVID-19-related reasons.

### Clinical measures

The clinical measures of immune reconstitution (CD4 >500/ $\mu$ L)<sup>53</sup> and viral suppression (mRNA <200 copies/ $\mu$ L)<sup>53</sup> will be assessed through change of CD4 cell counts from baseline; however, it is unlikely to observe

**Table 1** Feasibility measurements

Variables	Measure	Mode of administration	Weekly	Monthly	24 weeks
<b>Recruitment</b> <sup>55</sup>	No of subjects enrolled per month	Spreadsheet*		✓	
	No of recruitment calls made per enrollee	Spreadsheet*		✓	
	Proportion of new PLHIV successfully reached	Spreadsheet*		✓	
	Proportion of new PLHIV enrolled and randomised	Spreadsheet*		✓	
<b>Randomisation</b>	Balance achieved across two arms	Analysis†			✓
<b>Retention</b>	Proportion of participants with complete study data	Spreadsheet*			✓
<b>Intervention fidelity</b>	Adherence to per protocol delivery of text messages	Checklist‡	✓		
	Follow-up with patients per protocol	Checklist‡	✓		
	Provision of counselling when needed	Checklist‡	✓		
	Arranging referrals when needed	Checklist‡	✓		
<b>Intervention engagement</b>	Participant response rate within a 48-hour window <sup>49</sup>	Checklist‡	✓		
	No of times participants initiate messaging	Checklist‡	✓		
	Time of active participation in the study <sup>55</sup>	Checklist‡			✓

\*Track-sheet: Project leader will enter all data into tracking sheets.

†Analysis: postintervention analysis of sociodemographic and clinical data across study groups.

‡Checklist: The intervention facilitator and research assistants will have checklists.

PLHIV, people living with HIV.

an effect, given the short duration of the trial. Viral load tests are not included in the free national antiretroviral programme, and are offered in this trial as a benefit of participation at the conclusion of the trial; consequently, virologic suppression is measured at a single time point.

Psychosocial measures, treatment barriers and demographic factors are measured through the questionnaires listed in [table 2](#). These measurements will inform the study as they could be impacted by the intervention, or act as a mediator or moderator. The study is not powered

**Table 2** Trial measurements

Outcome measures		Baseline	6 Months
<b>Adherence to ART</b>	Wilson 3-item self-report scale on adherence <sup>51</sup>		✓
<b>Retention in care</b>	Missed visits and monthly visit constancy <sup>52</sup>		✓
<b>Viral load</b>	Virological suppression (<200 copies/μL) <sup>53</sup>		✓
<b>CD4 cell count</b>	Immune reconstitution, (>500/μL) <sup>53</sup>		✓
<b>Depression</b>	Patient Health Questionnaire-9 <sup>56</sup>	✓	✓
<b>Anxiety</b>	Hospital Anxiety and Depression Scale <sup>57 58</sup>	✓	✓
<b>Social support</b>	Multidimensional Scale Perceived Social Support <sup>59</sup>	✓	✓
<b>Stigma and disclosure</b>	The Berger stigma scale shortened and validated <sup>60</sup>	✓	✓
<b>Coping</b>	Coping responses <sup>61</sup>	✓	✓
<b>Drug use</b>	WHO-ASSIST <sup>62</sup>	✓	✓
<b>Beliefs</b>	Concerns and beliefs on ART necessity <sup>63</sup>	✓	✓
<b>Barriers</b>	Structural barriers to clinic attendance for ART patients <sup>64</sup>	✓	✓
<b>Demographic factors</b>	Age, gender, education, marital status, housing, household size, employment, income and poverty. These items are picked from Iranian Ministry of Health's demographic questionnaire.	✓	✓

ART, antiretroviral therapy.

to detect definitive effect sizes, but any change in direction would likely inform the future definitive trial.

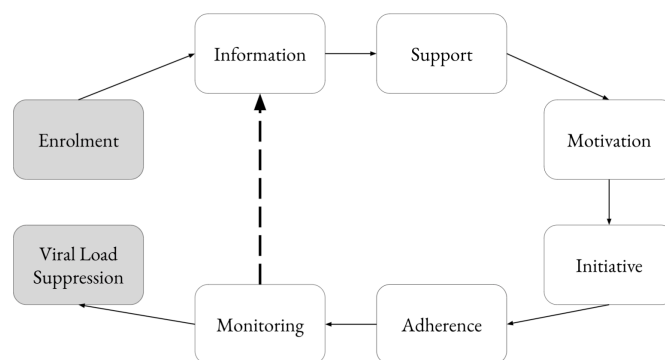
### Data analysis

To assess the feasibility of the trial, a descriptive data analysis approach will be undertaken. Participant flow will be summarised, reporting the proportion of recently diagnosed PLHIV who were eligible to participate from the list of those who are new patients under the care of the VCT centre, and those of which who were reached, screened, enrolled and randomised, respectively. Following randomisation, the rate of retention of participants will be used to assess potential for bias and the representativeness of the final analytic sample. Baseline characteristics will be compared between participants and eligible PLHIV who did not participate utilising clinic files, using Cochran Mantel-Haenszel  $\chi^2$  tests for categorical variables and Student's t-tests for continuous variables. Comparisons will also be made between intervention versus comparison participants to assess randomisation, and between those who completed the intervention vs those lost to follow-up. A descriptive analysis of the outcome measures for intervention fidelity, intervention engagement and acceptability will be summarised. All analyses will be conducted using the R programming software.

The pilot trial will be reported using Consolidated Standards of Reporting Trials guidelines on standards of reporting randomised trials. All randomised participants will be included in analyses. We will perform both intention-to-treat and per-protocol analyses. Given the pilot nature of this study, all analyses will be non-confirmatory. To generate preliminary data on the efficacy of HamRaah, univariate logistic and linear regression models will be used for dichotomous (retention and viral suppression) and continuous (adherence and CD4 Cell count) outcomes respectively. For the main dichotomous outcome ( $\geq 95\%$  adherence after the 6-month intervention), risk differences and 95% CIs will be calculated. Achieving undetectable viral load will be similarly treated as a dichotomous outcome. Estimates of effect sizes for the differences between HamRaah and comparison groups will be used to perform calculations of sample sizes needed for a future definitive randomised controlled trial. To examine interrelationships among adherence and other psychosocial measures, bivariate Pearson correlations will also be explored. Given the limited statistical power, subgroup analyses will be exploratory only.

The acceptability study aims to focus on participant perceptions regarding the cultural and logistic appropriateness of HamRaah, and the burden of the intervention. The research question will aim to answer whether HamRaah fits the personal, cultural and social contexts of new PLHIV, and whether the intervention was useful in ways that may have not been captured via the quantitative measures.

The nested realist evaluation will use a theory-driven approach and aims to examine why, how, for whom, and



**Figure 4** Realist programme theory.

in what context the intervention is effective. The process will be informed by the initial programme theory, which is depicted in figure 4 and was informed by an initial qualitative study. The theory highlights the resources that can be modified through mHealth during the lifetime of ART, and it guides how (if at all) HamRaah will change the context and impact these steps in a way that could explain the intervention mechanism(s) for future trials.

The realist evaluation and acceptability study will both be embedded into the intervention arm of the trial, and qualitative interviews and FGDs will begin following participants' completion of the intervention.

All qualitative data will be managed through MAXQDA. The data sets will be synthesised drawing on the principles of realist evaluations, generating context-mechanism-outcome configurations to enrich and refine the initial programme theory. This will contribute to better understanding of the mechanism of HamRaah and the role of context.

In a sequential triangulation approach, the hypotheses arising from the realist and qualitative findings will be tested in a second quantitative step, using the collected psychosocial measures, for exploring preliminary changes on mediating factors. The results will inform future investigations in the planned larger trial.

### Patient and public involvement

Decisions regarding the intervention, such as two-way versus one-way, and frequency of, messaging, were made in consultation with PLHIV and the healthcare team in the qualitative phase to ensure that the intervention is low burden and suited to context of PLHIV needs. Similarly, decisions regarding trial conduct were made in consultation with patients. These decisions included offering free viral load tests as a benefit of participation, optionality on which messaging application to receive HamRaah, and both online and offline means of completing the questionnaires. Moreover, research assistants, leading the recruitment, enrolment and interviewing of participants are members of the PLHIV community. Per the research plan, the results of the trial will be disseminated in a report format to all participants via mobile messaging, in the spirit of HamRaah.



## ETHICS AND DISSEMINATION

### Ethical considerations

The HIV epidemic in Iran is heavily concentrated among people who use drugs, sex workers, transgendered populations and men who have sex with men. In Iran, research conducted with such populations and approved by local ethics committee benefits from full confidentiality. Access to medical care is not restricted for these populations who are protected by doctor–patient confidentiality. However, special care and consideration needs to be applied in order to protect patient confidentiality, especially considering the limitations in controlling the faith of text messages. Messages may be read by persons other than the intended recipient, can easily be forwarded and could remain resident on unsecured devices for the lifetime of the technology. Text messages containing reminders to take medications, for example, could result in unintended disclosure of a medical condition even without specifying any details. To address this issue, following extensive consultation with the local institution, it was decided that the study would exclude participants who do not consent to receiving HIV-related communication on their phones due to concerns regarding unintended disclosure. As such, the risk of such disclosure will be minimised for study purposes. Moreover, potential social harms will be investigated to arrange counselling services as needed. Finally, the following steps will be taken to further minimise these risks:

- i. No direct mention of HIV will be included in the initial message. Only if patient initiates direct questions on HIV, would the counsellor follow-up with providing HIV-specific information.
- ii. Messaging intervention will be delivered through WhatsApp, Telegram or Signal, which are fully encrypted. Participants will choose a nickname to be used for chatting with the counsellor.
- iii. To safeguard patient privacy, the option is given to choose a pin, which they will share with the staff on initiation of conversation to ensure that counsellor is not in contact with a third party.
- iii. Participants can choose to discontinue participation at any point, and the study team will be responsible to ensure no harm is inflicted on the study population as a result of their participation in the trial.

No financial rewards will be given for participation to avoid coercive appeal for participation. A free viral load test at the conclusion of the study will be offered as benefit of participation. A warm meal will be provided in appreciation of participation on presenting for final assessment, focus groups and interviews. However, in light of the COVID-19 pandemic, arrangements to provide a meal-card for a food delivery service will be offered.

### Ethical approval

The study has received ethical clearance from Tehran University of Medical Sciences and Oxford Tropical Research Ethics Committee. The funding for the study

has been secured through the Tehran University of Medical Sciences research fund.

### Data transfer and storage

Study data are collected and managed using REDCap tools hosted at Partners Healthcare.<sup>12</sup> REDCap is a secure, SSL encrypted, web-based software platform designed to support data capture for research studies. The survey link is a singular URL to the survey, which does not track IP addresses, email addresses or any other identifying information. No identifiable questions will be included in the survey items. The data will be stored in the secure servers of REDCap, and the anonymised data will be exported to the research group in the chosen file format.

FGDs and in-depth interviews will be recorded with the consent of participants. The informed consent forms will include participants' full names and signatures, but these will not be collected by the administrator of the focus groups and/or interviews. As such, all recordings of the discussions and interviews will not contain personal identifiers, such as full names. The audio recordings of participants' voices will be transcribed. However, the transcription process will deliberately not transcribe any of the identifying information, in the event that any personal identifiers are disclosed. As such, no information with personal identifiers will be stored or accessible following transcription of the recordings.

All data, both from qualitative interviews and quantitative surveys, will be accessible to the primary investigator, who will share deidentified data with coinvestigators as needed only for analysis purposes.

### Dissemination

The results will be disseminated at several levels, including PLHIV, peer supporters, practitioners, researchers, health-care organisations, and policy and programme stakeholders. Annual reports to TUMS research committee will be provided, in addition to presentations at IRCHA for the local stakeholders and representatives from the community of PLHIV in Tehran. Dissemination will also include peer-reviewed journal publications and presentations at national and international conferences. It is also hoped that the results of the trial will be disseminated in a report format to all participants via mobile messaging, in the spirit of HamRaah.

### Declaration of interests

There are no conflicts of interest disclosed.

## DISCUSSION

This study is the first to explore the potential of mHealth to improve PLHIV's treatment adherence in a MENA country. Given the known relationship between adherence to ART and viral load suppression,<sup>54</sup> the results will further shed light on the potential of mHealth to suppress viral load within the first year of HIV diagnosis. The results of this study will provide important

information with respect to feasibility and acceptability of mHealth within the HIV care structure of Iran. Findings will inform the implementation of a larger definitive trial, which could apply a multicity design. The embedded realist evaluation will shed light on the mechanism of the intervention; how, for whom, in what context and why the programme is effective.

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**Contributors** VA conceived the study, drafted and finalised the manuscript. VA and MM are the grant holders of this study. VA, JH and LS contextualised mHealth for Tehran, Iran and developed the protocol of HamRaah. JH, LS, FM and JB provided critical input to finalise the protocol for this pilot trial and evaluation. Finally, JH, LS, FM, JB, LT and MM contributed to this study and this manuscript by critically commenting and approving the final manuscript.

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## Appendix

### **Additional Information on the Research Setting:**

The infectious diseases unit of Imam Khomeini Hospital Complex (IKHC) includes 13 physicians, who are faculty members at TUMS and members of the Iranian Academy of Sciences, serving as advisors for health programming and guideline development. Additionally, 17 residents specialising in infectious diseases and 32 nurses staff the infectious diseases unit. The VCT centre, which is mainly focused on HIV and other sexually transmitted diseases, includes a team of four physicians and two counsellors. The Positive Club is under the oversight of the VCT centre. IRCHA and its 8 full-time researchers and research assistants collaborate with the VCT and the positive club.

### **Additional Information on Routine Care:**

Patients are expected to visit the clinic monthly to receive free medication refills and clinical examinations. Counselling on adherence is offered to patients who miss monthly visits or report problems with medication adherence, viral suppression, or treatment resistance. As part of the routine care, a mandatory check-up with an infectious disease specialist is also offered every three months for patients with clinical signs of non-adherence or signs of irregular medication pick up. The Positive Club offers additional counselling and support, on referral, for PLHIV who are facing adherence or psychosocial difficulties. The intervention group will also receive these routine services, in addition to the HamRaah intervention, which includes independent counsellors to prevent risk of contamination.

### **Additional Information on HamRaah Intervention:**

When contact is triggered, the counsellor will enquire about the problems the patient may be facing, or the reasons for missing doses. The counsellor will be selected from the pool of locally trained psychologists, most of whom receive CBT training, to ensure PLHIV are treated sensitively and professionally on the phone. As such, the intervention is not meant to provide CBT through messaging, but rather differentiate patients who may need a one-time over-the-phone support from those who need to be referred for additional and more long-term support. However, if long-term support is needed, the counsellor, familiar with IKHC resources, will refer the patient according and tailored to his/her needs to further services, in such a way to ensure HamRaah is boosting access to



## Appendix

available healthcare capacities. For example, patients who are facing mental health challenges will be encouraged to accept a referral to counselling to help patients address any emotional or cognitive barriers to ART use. Additionally, they could be linked to the peer-support offered at the Positive Club, which also provides educational, motivational, and skill-building classes, and where both PLHIV and trained psychologists operate a variety of weekly classes to help patients address barriers to adherence through problem solving and encouraging good habit formation. In cases where medical counselling and clinical treatment are necessary, appropriate referrals are offered.

Thus, HamRaah aims to promote adherence to ART as primary outcome. It also aims to streamline the process through which newly diagnosed PLHIV access available health services that meet their needs in a timely window, before critical care becomes necessary. The weekly check-in schedule could also prevent prolonged gaps in adherence that increase the risk of viral rebound. It also seeks to promote good medication-taking habits to achieve optimal longer-term outcomes.